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Have Radiographic Progression Rates in Early Rheumatoid Arthritis Changed? A Systematic Review and Meta-analysis of Long-term Cohorts

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Abstract

Objectives

The objectives of this systematic review are to evaluate firstly, all published data on baseline and annual progression rates of radiographic damage from all longitudinal observational cohorts, and secondly, the association of standard clinical and laboratory parameters with long-term radiographic joint damage.

Methods

A comprehensive search of the literature from 1975 to 2014, using PubMed, SCOPUS and Cochrane databases, identified a total of 28 studies that investigated long-term radiographic progression, and 41 studies investigating predictors of long-term radiographic progression. This was submitted and approved by PROSPERO in February 2014 (Registration Number: CRD42014007589).

Results

Meta-analysis indicated an overall baseline rate of 2.02%, and a yearly increase of 1.08% of maximum damage. Stratified analysis found that baseline radiographic scores did not differ significantly between cohorts recruiting patient's pre and

post 1990 (2.01% vs. 2.03%; $p>0.01$), however the annual rate of progression was significantly reduced in the post 1990 cohorts (0.68% vs. 1.50%; $p<0.05$). High levels of acute phase markers, baseline radiographic damage, anti-CCP and Rheumatoid Factor positivity remain consistently predictive of long-term radiographic joint damage.

Conclusions

Critical changes in treatment practices over the last three decades are likely to explain the reduction in the long-term progression of structural joint damage.

Acute phase markers and presence of Rheumatoid Factor/anti-CCP are strongly associated with increased radiographic progression.

Introduction

Radiographic damage is an important outcome in observational studies and clinical trials in Rheumatoid Arthritis (RA). Chronic synovitis in RA results in irreversible bone and cartilage destruction(1). Erosions are indicators of failure to control the disease(2,3) that are associated with increased pain and functional disability(4,5).

Previous systematic reviews have shown(5,6) 39-73% of early RA patients to develop one or more erosions in the first 5-years, with radiographic damage progressing at a constant rate for the first 20-years of the disease(5). Subsequent systematic reviews(4,7) concentrated on specific predictors (functional assessment and disease activity indices) and their relationship with radiological damage.

However, to date no review has used quantitative analysis techniques, including meta-analysis, to investigate radiographic progression rates.

As structural damage is irreversible(5,8), it would be advantageous to identify patients at higher risk of severe damage so their treatment could be tailored

earlier on. Predictive modelling is a relevant statistical method to identify factors associated with primary RA outcomes(8,9). Previous studies have highlighted relationships between radiographic progression and functional disability(4) and disease activity (7). Other factors like anti-CCP antibodies and genetic factors have yet to be fully reviewed.

In this systematic review we have evaluated published data on baseline and annual progression rates of radiographic damage from longitudinal observational cohorts, and defined their association with standard clinical and laboratory variables. To date, this is the first review to use appropriate meta-analysis techniques to evaluate both the baseline and annual progression rates of radiographic joint damage scores, as well as the predictive markers identified, for all long-term observation cohort studies.

Methods

A systematic review protocol was developed to ensure the objectives and aims were outlined from the outset. This was approved by PROSPERO in February 2014 (CRD42014007589) (PubMed Search in Supplementary Data 1).

Identifying publications

Publications were identified by computerised searches of PubMed, Cochrane Library (incl CENTRAL, CDSR, DARE, HTA) and Scopus. Additional lateral search techniques included checking reference lists, performing key word searches in Google Scholar and using the 'cited by' option in PubMed. Databases were searched from January 1st 1975 to February 31st 2014. The search strategy used key words and MeSH terms on the title/abstract and full text as appropriate.

Inclusion/exclusion criteria

Inclusion criteria to select publications comprised of: (1) investigated the progression or predictive/prognostic markers of radiographic joint damage, (2) patients had a diagnosis of RA, using validated classification criteria like the

European League Against Rheumatology (EULAR) and/or the American College of Rheumatology (ACR) criteria, (3) baseline assessments occurred no later than 3-years from symptom onset, (4) prospective cohort study design, (5) radiographic follow-up data available for at least 5-years for progression rates, and 3-years for predictive markers, (6) used Larsen or Sharp van der Heijde method (SvdH) to score radiographic damage, and (7) only publications in English.

Publication screening

One reviewer (LC) screened titles/abstracts identified in searches, using the selection criteria to identify potentially relevant papers. A second reviewer (EN) independently screened the full text of 10% of all publications identified against agreed inclusion criteria. Agreement was achieved in 97% with disagreements resolved through discussion. Supplementary Figure 1 shows publications identified, screened and included in this review.

Data extraction

Two reviewers (LC and RS) extracted data using a pre-designed form, piloted to ensure all data necessary was captured. It included: cohort name, country of study population, scoring method used, number of patients included, years of recruitment, length of follow-up, sex, mean age, baseline DAS and HAQ scores, proportion of patients on DMARDS, proportion RF positive, number, mean/median and standard deviation/interquartile range of radiographic scores at each follow-up visit, analysis method used, significant and non-significant predictors identified the effect estimate and 95% confidence intervals. In cases where the raw data were not given in the published paper, the author was contacted to provide this data (n=21).

Quality Assessment

Studies were rated using the Downs and Blacks instrument for non-randomised studies of health care interventions(10). Since the studies did not examine clinical effectiveness, checklist items related to comparative groups (e.g. randomisation and blinding procedures) were omitted. One reviewer (LC) scored all studies using the amended checklist and another reviewer (RS) independently scored 10% of

studies drawn at random. Discrepancies between reviewers were discussed and consensus achieved.

Analysis

Means and standard deviations of the Larsen or Sharp score were recorded at each follow-up time for each study. In cases where only a median score was obtained, the median and range was converted into a mean score and standard deviation(11). To estimate annual rates of change, with standard errors, a linear regression model was conducted with follow-up year as the independent variable. Baseline scores and annuals progression rates, with respective standard errors, where transformed into percentage maximum damage for each scoring method (12,13). Transformed scores were entered into random effects meta-analysis to calculate pooled effect estimates for both baseline radiographic scores and annual rate of change.

To assess the strength of predictive markers, the regression coefficients and odds ratios (OR), with 95% confidence intervals, were collated. Unadjusted effect

estimates was sought. Where these were not reported the adjusted estimates were used. Random effects meta-analysis was used for all models due to the likely high level of heterogeneity between studies. Analysis used Stata (version 13); significance was assumed at $p < 0.05$.

Heterogeneity

The study entry criteria aimed to include studies as homogenous as possible to allow appropriate meta-analysis. Heterogeneity between studies was predicted a priori, mainly due to differences in when cohorts started and differences in scoring methods. The i-Squared statistic for each model was found to be consistently above 80%, and therefore random effects models were used throughout. To investigate possible sources of heterogeneity, scoring method and recruitment year were entered into meta-regression models and were the basis of two separate stratified analyses. Given the low level of studies included in the analysis, the ten studies were stratified into two recruitment period groups, 1965–1989 and 1990–2000. This provided equal groupings for stratified analysis. In addition, this marked a change in the clinical management of RA, were from 1990

the focus moved toward treat-to-target, with more intensive treatment within the first three months of disease.

Narrative Synthesis of predictive factors

Identified markers were recorded and counted to ascertain common associations with a separate count of significant predictors. Where possible, meta-analysis was used to assess the strength of predictive markers. However, for several predictive markers meta-analysis was not possible as too few studies reported results that could be pooled. When meta-analysis was inappropriate a narrative synthesis of the data was conducted.

Results

Meta-analysis of long-term radiographic progression

Of the 28 studies identified, ten provided the necessary data for meta-analysis(14–22) (Table 1). Patients were recruited from 1965-2000 and follow-up ranged from 5-20 years. The number of patients included with baseline radiographic data ranged from 73-1121. Four studies used Larsen; six used the SvdH scores. Five recruited patients from 1965-1989 and five from 1990-2000.

Table 1. Summary of cohorts stratified by recruitment year

Baseline radiographic score

The first analysis examined baseline radiographic score across all studies. The overall rate of damage at baseline was estimated at 2.02% (95% CI 1.37-2.67) of maximum damage. The sub-group pooled estimate for Larsen score was 3.41% (95% CI 1.80-5.01) of maximum damage (6.82 units); the sub-group pooled estimate for the SvdH score was 1.20% (95% CI 0.60-1.80) of maximum damage (5.38 units). Studies recruiting patients between 1965-1989 had a sub-group

pooled estimate of 2.01% (95% CI 1.14-2.89) of maximum damage; studies recruiting between 1990-2000 reported a sub-group pooled estimate of 2.03% (95% CI 1.05-3.01) of maximum damage (See Figure 1).

Title: Baseline Radiographic Score Pre and Post 1990

Caption: Figure 1. Forest plot of baseline radiographic scores stratified by recruitment periods

Annual rate of change

In the second analysis overall annual rate of change was estimated at 1.08% (95% CI 0.72-1.44) of maximum damage. The sub-group pooled estimate for Larsen score was 1.38% (95% CI 1.80-5.01) of maximum damage (2.76 units/year); the SvdH score was 1.20% (95% CI 0.88-1.88) of maximum damage (4.03 units/year). Studies recruiting patients between 1965-1989 patients had a sub-group pooled estimate of 1.50% (95% CI 1.08-1.92) of maximum damage; for 1990-2000 it was 0.68% (95% CI 0.47-0.90) of maximum damage (Figure 2).

Title: Annual Rate of Radiographic Progression Pre and Post 1990

Caption: Figure 2. Forest plot of annual rates of change stratified by recruitment periods

Meta-Regression

The small sample size (10 studies) limited the power to conduct meta-regression models with an appropriate number of covariates; however, it was important to investigate possible factors influencing the overall effect estimate given the high levels of heterogeneity between studies (i-squared score ranging from 90.5%-98.3%).

The meta-regression indicated that there was a statistically non-significant difference for baseline progression rates between recruitment periods ($p > 0.1$), but a statistically significant difference for annual progression rates between recruitment periods ($p < 0.05$), whilst controlling for scoring method. The models indicated that differences between Larsen and SvdH scoring methods were not

statistically significantly different for annual progression rates ($p>0.1$), suggesting relative increases in either scoring method was comparable. Scoring method was a statistically significant factor for baseline progression rates ($p<0.05$).

Review of predictive markers of long-term radiographic damage

Forty-one papers were identified that examined predictive markers of radiographic joint damage, representing 21 cohort studies. Although several papers were based on the same cohort data (Table 2), the analysis techniques used were sufficiently different from each other to allow their inclusion in the analysis.

Table 2. Table of studies investigating predictors of radiographic progression

Twenty-eight studies used the SvdH (23,15,24–26,19,27–30,21,31–46,1); 13 used the Larsen scoring method (47–49,20,50–58). Twenty-four of 41 studies examined radiographic damage at a single time point, whilst 17 investigated radiographic damage expressed as a change in score over two time points. Thirteen studies

transformed radiographic scores into binary variables and 27 treated the radiographic score as a continuous score. One study treated the radiographic score as an 'event' in a 'time-to-event' analysis(53). Overall 12 different analysis methods were used (Table 2).

Title: Number of Significant and Non-Significant Predictive Factors

Caption: Figure 3. Number of significant and non-significant predictive factors

Acute phase Markers

Acute phase markers (ESR or CRP) were one of the most frequently reported covariates (See Figure 3). Fifteen studies included the ESR and 13 found it was a statistically significant predictor. Eleven studies included CRP and 10 found it was a statistically significant predictor. Although there was sufficient data to conduct a meta-analysis, large intra-study differences on how acute phase markers were evaluated made formal meta-analysis inappropriate. While studies assessed acute phase markers as continuous predictors; other used them as categorical

predictors, either using pre-defined cut-points or using quartiles. This made direct comparison between the effect estimates unfeasible.

Courvoisier et al.(15) reported increased ESR indicated over a three-fold increase risk of a radiological damage score above the median at 10 years. Similar effect estimates were seen in other studies using similar analysis techniques. An odds ratio (OR) of 2.7 (CIs not given) was reported by Fex et al.(48) and an OR of 2.9 (95% CI 1.01-5.88) was reported by Tanaka et al.(21). Similarly Bukhari et al.(23) reported an Incidence Rate Ratio (IRR) of 2.0 (95% CI 1.4-3.0). Using linear regression techniques, Lindqvist et al.(51) reported an average increase of 0.42 (95% CI 0.62-1.04) units of the Larsen Score for every one-unit increase in CRP. Mustila et al.(52) reported only ESR was significantly associated with radiographic joint damage at 12, 36, 60 and 84-months in univariate analysis, whereas RF was only statistically significant at 36-months, and perinuclear Antineutrophil Cytoplasmic Antibodies (pANCA), Antikeratin Antibodies (AKA), Antiperinuclear Factor (APF) and Age were not associated at any time.

Anti-Cyclic Protein Antibodies (ACPA) and Rheumatoid Factor (RF)

ACPA, largely anti-CCP, was evaluated in 16 studies and 14 of these reported statistically significant associations. Using linear regression, Lindqvist et al.(51) reported patients positive for anti-CCP had on average an increase of 37 units on the Larsen score compared to anti-CCP negative patients over 10 years. Nyhäll-Wåhlin et al.(30) reported an increase of 14.74 over 5 years. Anti-CCP positive patients were also reported to have between a 2.3 and 9.3 fold increase in risk of rapid radiological progression(24,25).

The predictive role of RF was evaluated in 21 studies and 12 reported statistical significance. Four studies investigating radiographic progression based on low or high radiographic damage groups showed RF positive patients were 1.8-2.8 times more likely to have high rates of long-term radiographic joint damage(21,23,24,55).

To assess the relative strength of anti-CCP and RF, studies reporting OR and 95% confidence intervals were entered into a random effects meta-analysis. Five out of

the 13 studies reporting anti-CCP and 10/21 studies reporting RF were included in the meta-analysis. Reasons for exclusion comprised insufficient data, lack of data on measures of variation and no calculated ORs. The overall pooled effect estimate for anti-CCP was 2.49 (95% CI 1.96-3.15) and for RF was 2.07 (95% CI 1.61-2.65) (Figure 4). These findings suggest a moderate difference between the two markers, with anti-CCP more strongly associated; but overlapping 95% CIs suggest this difference is statistically non-significant. All five studies included in the meta-analysis for anti-CCP showed an increased risk. Only one reported a statistically non-significant result, which was also the only adjusted effect estimate included (49). All but two studies included in the RF analysis reported an increased risk (28,49).

Title: Forest Plot of Anti-CCP, RF and HLA-DRB1

Caption: Figure 4 – Forest plot of Anti-CCP, RF and HLA-DRB1

Genetic Factors

Sixteen studies investigated the influence of genetic factors on radiographic progression and 12 reported statistically significant associations. Four studies used follow-up data of ≥ 5 years; 12 were restricted to 3-4 years follow-up. ORs for the presence of HLA-DRB1-SE ranged between 1.31 and 2.6(23,24,34). Two studies by Constantin et al showed HLA-DRB1 was associated with increased radiographic progression over 4 years(35,36).

Seven of the 16 studies provided sufficient data for meta-analysis. A random effects model showed an overall pooled estimate of 1.53 (95% CI 1.09-2.14) (Figure 4). Two of the 7 studies reported a decreased risk (15,40).

Other factors

There was limited evidence that age and female sex predicted radiographic joint damage. Only 4/12 and 4/15 studies respectively reported statistically significant findings. The reported effect sizes of both age and sex were low: age gave 1.14(24) to 1.2(23) times increase in risk, while female sex reduced risk by 25% (24). Few studies evaluated joint counts, Disease Activity Score, pANCA, MMP-3

and functional disability making it impractical to draw conclusions about their impact on radiographic damage or to undertake meta-analyses.

Quality Assessment

All studies were assessed for quality using the Downs and Blacks Quality Assessment Checklist (10) (Supplementary Figure 2 and Supplementary Table 1).

Most studies were of good quality. All studies reported clear aims, objectives and outcome measures and recruited representative patients. Only 3 studies (6%) reported on missing data and only 7 (15%) reported on losses to follow-up. The use of appropriate statistical methods was also lacking, particularly in the 3-5 year follow-up predictive studies, where only 13 studies (27%) used appropriate statistical methods.

Discussion

This review is the first to use meta-analysis techniques to provide accurate estimates of overall radiographic damage at presentation and over a 20-year period in early RA patients. Data from 10 studies shows the overall radiographic damage rate at presentation was 2.02% of maximum damage, and the overall annual progression rate was 1.08% of maximum damage.

Previous reports(5) estimated total annual radiographic progression rates were 1.9% of maximum damage; the Larsen score progressed 3.8 units/year (2.5% maximum damage) and SvdH score progressed 4.3 units/year (1.3% maximum damage) over the first 15 years. The present study found similar rates with an overall progression rate of 1.08% (95% CI 0.72-1.44) of maximum damage. Split by scoring method, the Larsen score progressed 2.76 units/year (1.38% maximum damage), and the SvdH score progressed 4.03 units/year (1.20% maximum damage) over the first 20-years of disease. The differences in rates between our findings and previous reports (5) are likely to be multifaceted. Firstly, meta-analytical techniques to calculate pooled effect estimates give different rates than

relying on averages. Meta-analysis is a more robust method as larger studies are given a higher weighting, reducing the influence of less precise estimates from smaller studies; it also estimates precision (95% confidence intervals). Secondly, our inclusion criteria focussed on observational cohorts of early RA patients. This ensured a more homogenous study sample as patients in RCTs are highly selected with higher levels of disease activity and higher rates of radiographic progression(13,40). This review studied patients from 'true-to-life' clinical settings.

Stratifying studies by recruitment year showed annual progression rates in studies recruiting between 1990-2000 was more than half the rate reported in studies recruiting between 1965-1989. However, baseline radiographic damage was similar across both recruitment periods. The reduction in radiographic progression from 1965-2000 is concordant with data from Finckh et al (59), who found decreased progression rates from 1970-1990, and Sokka et al (54), who found decreased 5-year radiographic progression rates across three cohorts (1983-1985, 1988-1989 and 1995-1996). Finckh et al.(59) suggested this was a consequence of more intensive therapies as the temporal effect diminished after

controlling for DMARD use. More recent data from RCTs show combinations of synthetic Disease Modifying Anti-rheumatic Drugs (DMARDs) and biologics are highly effective in slowing radiographic progression (60), particularly during the 'Window of Opportunity'(12). Reduced rates of radiographic progression was also seen in a systematic review of RCTs, where more recent RCTs of patients on methotrexate had less radiographic progression compared to RCTs conducted earlier(61).

Differences between the two recruitment periods in our review also coincides with changes in clinical management, particularly more intensive treatment in the 1990s with methotrexate the anchor DMARD(62). Pincus et al.(62) reported that improvements in radiographic outcomes from 1985 to 2000 were associated with better joint scores, functional capacity and mortality outcomes. How much of these changes should be attributed to better treatment strategies however, remains uncertain due to the non-randomised study designs(54,62).

Interestingly there is an apparent dearth of new large observational cohort studies of new unselected RA patients. One factor could be the development of national registers of patients treated with biologics, which diverted expertise away from other observational cohorts. Other factors include continuing recruitment to observational studies and less emphasis on collecting radiographic assessments.

The predictive factors we identified is in agreement with previous findings(5) including the importance of acute phase markers and RF positivity. This review also found evidence for the association between anti-CCP positivity and long-term radiological damage. Navarro-Compán et al (7) assessed the relationship between radiographic joint damage and Disease Activity Indices (DAI) like the Disease Activity Score (DAS). It would appear that while DAIs are clinically useful, the individual components of the DAI's, particularly SJC and acute phase markers, were better predictors.

Our review is the first to summarise associations of anti-CCP and genetic factors with radiographic progression in long-term cohort studies. De Rooy et al(24)

found HLA-DRB1 shared epitopes increases the risk of radiographic joint damage at 5-years, but they did not include anti-CCP in their models. Recent studies(63,64) highlight the importance on the dependence of RA-related genetic markers on anti-CCP for associations with radiographic progression. Kaltenhauser et al.(49) reported that anti-CCP and DRB1*04 SE, used as a compound marker, was statistically significantly associated with increased radiographic damage at 4-years. However, Kroot et al.(26) found anti-CCP but not HLA-DRB4 was statistically significantly associated in multivariate analysis. This evidence suggests an association between SE-positive alleles and anti-CCP antibodies, though the pathogenetic mechanisms remain unclear(49). Further study of specific HLA-DRB1 haplotypes may show a prognostic role(63). Currently, genetic markers do not provide much additional prognostic information that can be applied clinically.

Several studies included in our review(28,46,49) found RF was not a significant predictor in the presence of anti-CCP, suggesting anti-CCP is the superior marker of long-term radiographic damage. Our meta-analysis suggests that anti-CCP could be more highly associated with increased radiographic damage. However,

differences in specific RF antibodies and titre levels may explain variations between studies.

The heterogeneity of the methods and analysis techniques used meant it was impossible to conduct a formal meta-analysis on all predictive markers to allow a direct aggregation of these results. One challenge in comparing studies related to differences in study design(65). When investigating novel markers in the absence of multivariate methods, the importance of well-established factors like seropositivity and acute phase reactants may not be appropriately considered. Consequently the effect of novel markers may be masked, or over-exaggerated when already established factors are not considered (9). Novel markers like MMP-3(25,53) have potentially strong associations with radiographic joint damage, but more evidence is needed with large patient samples using appropriate multivariate modelling techniques.

Another limitation is that it was not possible to stratify patients using disease markers like seropositivity when modelling radiographic progression rates, since it

would require more detailed and complex data from each cohort, which would be unfeasible to obtain. Consequently, although the review highlighted the potential differences in radiographic progression in patients with anti-CCP positivity, we could not produce separate rates of radiographic progression for seropositive and seronegative RA patients. Furthermore, the direct impact of treatment could not be fully assessed. Evaluating recruitment years provides a surrogate marker of changes in treatment practices, but we could not directly model the effect of treatment. Nevertheless, it is likely patients received standard contemporary care based on published guidelines about treatment regimens from the time they were being studied.

We conclude the progression of radiographic damage has halved since 1990, with improved treatment providing the most likely cause. RF/anti-CCP, along with increased markers of acute phase reactants remain strongly associated with radiographic damage, however the value of other novel antibodies need further study. Finally, while the investigation of different haplotypes is proving hopeful,

currently the genetic data is of limited additional prognostic value independent of anti-CCP positivity.

Key Messages

- Progression of radiographic damage in 2002-2011 is significantly lower compared to 1986-2001 in early RA
- Acute phase markers and RF/anti-CCP positive RA remain important predictors of erosive disease in RA.
- Longitudinal-studies needed on whether Anti-CCP is superior to RF in predicting radiographic damage in RA

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